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To cite this article: David P. Piñero PhD (2015): Misdiagnosing Keratoconus, Expert Review of Ophthalmology, DOI: [10.1586/17469899.2016.1136215](https://doi.org/10.1586/17469899.2016.1136215)

To link to this article: <http://dx.doi.org/10.1586/17469899.2016.1136215>



Accepted author version posted online: 24 Dec 2015.



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Publisher: Taylor & Francis

Journal: *Expert Review of Ophthalmology*

DOI: 10.1586/17469899.2016.1136215

MISDIAGNOSING KERATOCONUS

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Abstract

Several diagnostic criteria have been defined for the detection of keratoconus and keratoconus suspect. Most of these criteria are based on the analysis of the anterior and posterior corneal topography and the aberrometric pattern. However, there are corneas without ectasia showing an abnormal topographic and aberrometric pattern compatible with keratoconus. These cases are defined as pseudokeratoconus and can lead to wrong clinical decisions. The main causes of pseudokeratoconus are measurement artefacts, instability of tear film, contact lens warpage and presence of opaque corneal areas or scars. Likewise, some pathological conditions, such as local corneal oedema or corneal inflammatory processes, can be also associated to pseudokeratoconus patterns. A comprehensive analysis of the medical history data and the performance of several clinical tests, including pachymetry or measurement of corneal biomechanical properties, are crucial to avoid misdiagnosing keratoconus.

Introduction

Keratoconus is an ectatic corneal disorder characterized by a usually progressive corneal thinning resulting in corneal protrusion, irregular astigmatism and decreased vision.¹ In this condition, the cornea adopts a conical shape as a result of the degeneration of the corneal stromal tissue and the subsequent biomechanical alteration.^{1,2} Although corneal topography has been considered a crucial tool for the diagnosis of keratoconus, other devices and parameters are also useful, especially in incipient or subclinical forms.^{3,4} Pachymetric, posterior corneal elevation, anterior chamber depth, aberrometric and corneal biomechanical data have demonstrated to be very useful for keratoconus diagnosis.⁴

Currently, the detection of moderate and advanced keratoconus is not a difficult task using corneal topography in combination with the analysis of biomicroscopic, retinoscopic and pachymetric signs.¹ A more difficult task is the detection of very early or preclinical stages of keratoconus and for this reason different approaches have been developed for such purpose.⁵⁻⁹ Specifically, the term “keratoconus suspect” was coined for defining those corneas without biomicroscopic keratoconic signs but subtle topographic features similar to early stages of keratoconus.¹⁰⁻¹³ Current advances in diagnostic technologies allow the clinician to detect almost all types of keratoconus.⁴ However, misdiagnosing keratoconus is still possible when an asymmetric anterior corneal topographic pattern similar to those of ectatic corneas is present.¹⁴⁻²² These topographic patterns are defined as pseudokeratoconus.¹⁴⁻²² The aim of the current review was to summarize the diagnostic criteria of keratoconus and keratoconus suspect based on the global consensus²³ and to define the potential sources of keratoconus misdiagnosis due to the presence pseudokeratoconus patterns and how to detect them.

Diagnosis of keratoconus

Anterior corneal profile

The typical topographic map of a keratoconus displays a well-delimited zone with a high dioptric value, surrounded by progressively decreasing curvature zones (Figure 1). Although the cone vertex can be located at the superior²⁴ and central portion of the cornea,²⁵ it is displaced in most of cases towards the lower mid-peripheral region.⁴ Therefore, the topographic map of the anterior corneal surface displays a vertical asymmetry, with the following peculiarities:

- Focal steepening located in the cone protrusion zone surrounded by concentric decreasing power zones.

- Infero-superior (I-S) asymmetry within the mid-peripheral cornea. Special attention should be taken when obtaining values of the I-S index above 1.4 D.

- Angling of the hemi-meridians in the bow-tie pattern. Keratoconus must be suspected especially when this angling exceeds 20 or 30 degrees in relation to the vertical meridian.

Different diagnostic approaches have been developed considering these peculiarities of the anterior corneal topographic profile in keratoconus, including the definition of specific indices (Table 1),²⁶⁻⁴⁰ neural networks^{34,41-43} and mathematical algorithms of corneal shape reconstruction.⁴⁴⁻⁴⁸ The digital analysis of the image of the Placido disks projected on the cornea has been also shown to be a valid tool for keratoconus diagnosis, avoiding the use of estimated data or parameters obtained indirectly.⁴⁹ In addition, the analysis of corneal asphericity (Q) has been shown to be of potential usefulness in the detection of keratoconus (Figure 1), as the anterior protrusion generates an increase of the corneal prolatism, with an associated negativization of Q.⁵⁰⁻⁵² More marked negative asphericity (significant prolateness) for the anterior corneal surface has been found in some studies comparing some topographic features of normal and keratoconus eyes.⁵⁰⁻⁵² Specifically, mean Q values of -0.29 ± 0.09 , -0.65 ± 0.27 , and

-1.18 ± 0.32 have been reported in a sample of normal, keratoconus grade I and keratoconus grade II eyes (Amsler-Krumeich classification), respectively.⁵²

Posterior corneal elevation in keratoconus

Significantly larger values of best fit sphere (BFS)^{10,12,53} and highest posterior elevation^{11,12,54} have been found in keratoconus (Figure 2). Schlegel¹² et al found in a sample of 48 keratoconus-suspect patients a mean maximum posterior elevation of $0.0288 \pm 0.0102 \mu\text{m}$ at 1 mm of radius from the centre using the scanning-slit technology. Fam and Lim⁵⁵ defined the posterior elevation ratio as the ratio of the maximum posterior elevation in the central 5-mm corneal zone to the BFS for the posterior cornea, obtaining a mean value for this ratio of 1.874 ± 0.532 in a sample of 43 keratoconus patients and of 1.103 ± 0.462 in a sample of 23 keratoconus suspects using also the scanning-slit technology.⁵⁵ For a cut-off point of 0.5122, these authors obtained sensitivity and specificity values of 99% and 95.2% for the detection of keratoconus.⁵⁵ De Sanctis and colleagues¹⁰ found cut-off values of the maximum posterior corneal elevation measured in the 5-mm central zone of $35 \mu\text{m}$ (sensitivity 97.3%, specificity 96.9%) and $29 \mu\text{m}$ (sensitivity 68%, specificity 90.8%) for the detection of clinical and subclinical keratoconus using a Scheimpflug photography-based system.

Corneal aberrometry

Higher amounts of vertical coma and larger values of coma-like root mean square (RMS) have been reported in patients with keratoconus or keratoconus suspect^{2,5,51,56-59} (Figure 3). Bühren et al⁵ found cut-off points of primary coma root mean square (RMS) of 0.555 (sensitivity 100%, specificity 98.4%) and $0.248 \mu\text{m}$ (sensitivity 100%, specificity 73.6%) for the detection of clinical and subclinical keratoconus, respectively. Similarly, the levels of primary coma have been also found to be significantly elevated in the posterior corneal surface.^{60,61} Nakagawa et al⁶⁰ found in a sample of 28 keratoconic eyes large amounts of primary coma in the anterior and posterior corneal surfaces (primary coma RMS anterior/posterior: 3.57

/ 0.87 μm), although coma from the posterior surface compensated partly for that from the anterior surface.

Pachymetric analysis in keratoconus

Current imaging technology allows the clinician to obtain pachymetric maps providing information point-by-point of the entire cornea.^{3,4} A more detailed and accurate control of the progression of an ectatic disorder can be performed with systems, such as those based on Scheimpflug photography, optical coherence tomographers or very high frequency ultrasonography systems.^{3,4} It should be considered that the term corneal topography is used for defining the 2-D analysis of the anterior corneal shape whereas corneal tomography is used for the examination of the front and back surfaces of the cornea, along with pachymetric mapping, considering it computes a three-dimensional image of the cornea.⁶²

Differences in the progression of corneal thickness from centre to periphery have been found between normal and clinical and subclinical keratoconus eyes.⁶³⁻⁶⁸ Saad and Gatine⁶⁶ found that the percentage of thickness increase from the thinnest point to the periphery measured using the scanning slit-technology as well as the percentage of variation of anterior and posterior curvatures over the entire cornea centered on the thinnest point were able to detect very mild forms of ectasia undetected by a Placido-based neural network program. Ambrosio et al⁶⁵ demonstrated that pachymetric progression indices obtained with the Pentacam system were better factors to differentiate between normal and keratoconic corneas than single-point pachymetric measurements. In addition, the analysis of the epithelial thickness profile (epithelial doughnut pachymetric pattern) has been shown to be also useful for keratoconus detection and characterization.⁶⁹

Corneal biomechanics in keratoconus

Two different systems are currently available for the analysis of corneal biomechanics in clinical practice: Ocular Response Analyzer (ORA) (Reichert) and CorVis ST system (Oculus).⁷⁰ Concerning the main biomechanical parameters provided by the ORA system,

corneal hysteresis (CH) and corneal resistance factor (CRF), they have shown moderate diagnostic ability for keratoconus detection.^{71,72} Fontes et al⁷² obtained a poor overall predictive accuracy of CH (cutoff, 9.64 mmHg; sensitivity, 87%; specificity, 65%; test accuracy, 74.83%) and CRF (cutoff, 9.60 mmHg; sensitivity, 90.5%; specificity, 66%; test accuracy, 76.97%) for detecting mild keratoconus. New parameters based on the analysis of the response signal curve obtained with the ORA system have improved the diagnostic ability of this device for keratoconus detection.⁷³ Regarding the CorVis ST system, some limitations in the diagnostic ability of the parameters provided by this device have been reported.⁷⁵⁻⁷⁷ Tian et al⁷⁵ found that the deformation amplitude was the best predictive parameter, with a sensitivity of 81.7%, although there was a significant overlap between keratoconic and normal corneas that ranged from 1.0 to 1.4 mm.

Pseudokeratoconus topographic pattern

Four different conditions can lead to the measurement of topographic patterns compatible with keratoconus that are not representing a real ectatic condition: measurement artefacts, instability of tear film, contact lens warpage and presence of corneal areas with a loss of transparency or scars. Pseudokeratoconus displays some topographic features that are compatible with keratoconus, including areas of local corneal steepening, significant negative corneal asphericity, high values of posterior corneal elevation and astigmatism, and abnormally increased levels of anterior and posterior corneal aberrations.¹⁴⁻²²

Pseudokeratoconus due to measurement artefacts

Some acquisition artefacts with currently available corneal topography systems and tomographers can lead to erroneous measurements and incorrect interpretations by the device used for corneal analysis. These artefacts can be generated by incorrect patient positioning during measurement. Hick and coauthors¹⁵ found that rotational misalignment during measurement with the scanning slit technology was able to induce corneal asymmetry on

elevation and curvature maps and, consequently, pseudokeratoconus patterns. Hubbe and Foulks²⁰ demonstrated that a change in relative steepness with a Placido disk topographer produced a pattern that mimics keratoconus that could be seen at deviations of less than 5 degrees in some patients. It has been also shown the influence of eyelids in the anterior corneal shape when performing continuing pressure on them due to different gaze positions.⁷⁸ Therefore, it is important to check and control the patient position during the topographic measurement and to take three consecutive measurements if possible in order to confirm the consistency of the measurements obtained.

Pseudokeratoconus due to tear film instability

Tear film alterations are one of the most relevant factors leading to artefacts in a topographic examination, especially in those analysing object patterns projected on the cornea. A low tear film quality (low scores of the break-up time, BUT) or quantity (low Schirmer test values) can be associated to alterations in the anterior corneal surface (Figure 5), such as epitheliopathies which can contribute to obtain altered topographic patterns.⁷⁹ Cheng et al¹⁶ reported the case of a patient with soft contact lens-induced keratopathy in which the slit scanning corneal topography showed features suggestive of keratoconus. It is then recommendable to perform the topographic acquisition after an eye blink and to confirm the consistency of measurement in cases of dry eye by taking three consecutive measurements.

Pseudokeratoconus due to contact lens warpage

Contact lens wear may alter significantly the anterior corneal topographic pattern, especially with rigid gas-permeable contact lenses. It should be considered that rigid gas-permeable contact lenses as well as some silicone hydrogels have a higher rigidity module and their bearing on the cornea can cause some transitory effect (Figure 5). Tseng et al⁸⁰ documented a case in which a diagnosis of suspect keratoconus was made based on the corneal topographic map in a hydrogel contact lens wearer. At 8 weeks after the cessation of the contact

lens wear, corneal topography showed a normal pattern, confirming that a corneal warpage was previously present mimicking keratoconus.⁸⁰

Pseudokeratoconus due to loss of corneal transparency or scars

As all available topographic systems are based on optical principles, the presence of corneal areas with a loss of transparency may also lead to the obtaining of wrong data, especially when measurements are obtained with the scanning slit technology. Furthermore, scars or leukomas can generate areas of local flattening with the corresponding steepening of the adjacent areas leading to a pattern of pseudokeratoconus (Figure 6). Therefore, it is important to consider the level of transparency of the cornea and the medical history of the patient when interpreting a corneal topographic map showing a pattern compatible with a keratoconus.

Pseudokeratoconus due to other causes

There are some pathological conditions that can lead to the presence of topographic patterns compatible with keratoconus that disappear when the condition is treated. Localized changes in corneal thickness due to endothelial-Descemet membrane disruption¹⁴ or inflammatory processes¹⁸ can induce a pseudokeratoconus topographic pattern. Likewise, Dursun et al¹⁸ demonstrated that chronic ocular rosacea can generate an inferior corneal thinning and high astigmatism associated to a pseudokeratoconus pattern. These authors suggested that the inferior pattern of thinning in rosacea may be related to chronic exposure of the inferior cornea to inflammatory and matrix-degrading factors in the inferior tear meniscus.¹⁸

Tools for avoiding misdiagnosing of keratoconus

The diagnosis of keratoconus should not only be based in the analysis of the topographic pattern of the anterior corneal surface as this can lead to misdiagnosing. Indeed, there is no topographic parameter providing 100% of sensitivity and specificity for the detection of keratoconus, especially in subclinical forms. The combination of several clinical tests is

essential for an accurate detection and a complete characterization of a case of keratoconus.⁴ The medical history of the patient must be considered before providing a final and consistent diagnosis of an ectatic condition. Likewise, other evaluations besides corneal topography and aberrometry should be considered for an adequate diagnosis of keratoconus, such as the evaluation of corneal thickness, biomechanical properties or volume.⁴ Recent research on keratoconus are focused on defining prediction models for the detection of keratoconus according to a variety of clinical parameters.⁴ Montalbán et al⁵⁰ found by means of logistic regression analysis that the 8-mm anterior shape factor, the anterior chamber depth, and the minimal corneal thickness were significant independent predictors of the presence of keratoconus ($p < 0.01$). With the same type of statistical analysis, Uçakhan et al⁸¹ found that the combined analysis of anterior and posterior corneal power, elevation, and thickness data provided by a Scheimpflug imaging device effectively discriminated between ectatic corneas and normal corneas. Kovacs and colleagues⁸² defined a threshold level of posterior corneal elevation (40 μm) and corneal thickness (450 μm) beyond which the level of corneal protrusion in keratoconus accelerates. All these predictive models confirm the relevance of corneal thickness in the detection of keratoconus.

Conclusions

In conclusion, there are topographic patterns with similar features compatible with keratoconus but not representing a real corneal ectatic condition that can lead to misdiagnosing keratoconus. These cases are defined as pseudokeratoconus and must be identified properly in order to avoid taking wrong clinical decisions. Measurement artefacts, the instability of the tear film, the presence of contact lens warpage and the presence of corneal areas with a loss of transparency or scars are the main causes of pseudokeratoconic patterns. Likewise, some pathological conditions affecting corneal thickness can be associated to topographic patterns compatible with keratoconus. Clinical analyses in these cases should be complemented with other clinical tests, such as pachymetry or measurement of corneal biomechanical properties,

and with a comprehensive analysis of medical history data in order to perform a correct clinical diagnosis.

EXPERT COMMENTARY:

Currently, advances in diagnostic technologies allow clinicians to perform more accurate diagnosis of keratoconus, even in its incipient stages. The combination of the analysis of the anterior and posterior corneal topographic map, the pachymetric profile, biomicroscopic signs and corneal biomechanical properties provides an integrated analysis of the corneal structure, minimizing the number of wrong diagnostic decisions in terms of keratoconus detection. In spite of all these advances, there is still a possibility of misdiagnosing keratoconus due mainly to the presence of anterior corneal topographic patterns similar to those of ectatic corneas, which are defined as pseudokeratoconus. Measurement artifacts, the instability of the tear film, the presence of contact lens warpage and the presence of corneal areas with a loss of transparency or scars are the main causes of this type of patterns. The combination of the analysis of corneal topography with other clinical tests is crucial to avoid this type of misdiagnosing.

FIVE-YEAR VIEW:

In next five years, the incidence of keratoconus misdiagnosis due to pseudokeratoconus patterns will be dramatically minimized as new topographic devices are being developed and introduced in clinical practice that combine different technologies to obtain more information about the corneal structure, not only the analysis of the anterior corneal topographic pattern. The diagnosis of keratoconus will be based on a concept of integrated analysis with the combination of different clinical parameters, not only on the analysis of corneal topography.

KEY ISSUES:

-Different diagnostic approaches have been developed for keratoconus considering the peculiarities of the anterior corneal topographic pattern in this condition, including the definition of specific indexes, neural networks and mathematical algorithms of corneal shape reconstruction.

-The analysis of the topographic profile of the posterior corneal surface has been also shown to be a useful tool for diagnosis of keratoconus, with significantly larger values of best fit sphere and highest elevation for this surface in this corneal condition.

-The level of vertical coma and coma-like aberrations can be used as additional criteria for the detection of keratoconus or keratoconus suspect.

-The analysis of corneal biomechanical properties with the Ocular Response Analyzer or the CorVis ST system can be useful for complementing the diagnosis of keratoconus, although the sensitivity and specificity for keratoconus detection of the biomechanical parameters provided by these instruments are somewhat limited.

-There are topographic patterns compatible with keratoconus, including areas of local corneal steepening and significant negative corneal asphericity, which are not representing a real ectatic condition. These patterns are defined as pseudokeratoconus.

-There are four factors leading to pseudokeratoconus topographic patterns: measurement artifacts, instability of tear film, contact lens warpage and presence of corneal areas with a loss of transparency or scars.

-There are some pathological conditions that can also lead to pseudokeratoconus patterns, especially when localized changes in corneal thickness are present due to endothelial-Descemet membrane disruption or inflammatory processes.

-Integrated analyses of the results of different clinical tests as well as of the medical history data are crucial to perform an appropriate diagnosis and to avoid misdiagnosing keratoconus.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Figure legends

Figure 1.- Sagittal curvature map of a keratoconus cornea obtained by a rotating Scheimpflug camera-based topography system.

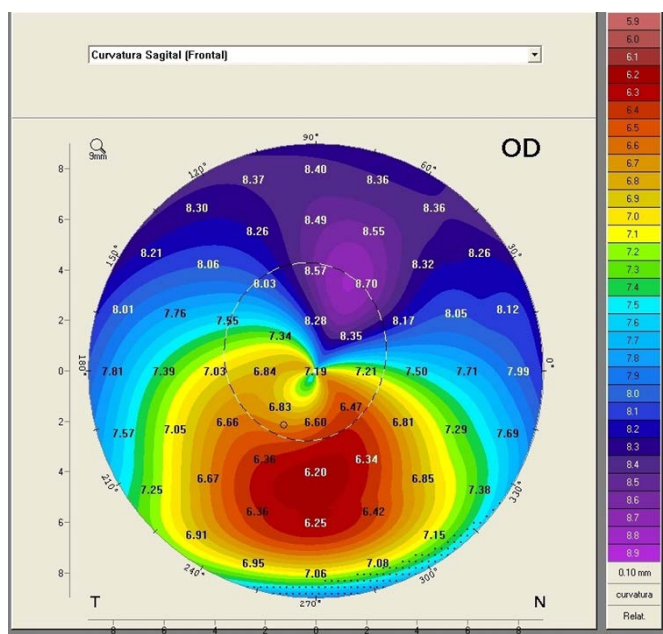


Figure 2.- Corneal analysis in a keratoconus eye with the Scheimpflug-based topography system Sirius from CSO (Italy). Four maps are displayed: pachymetric map (up-left), anterior tangential map (up-right), anterior elevation map (down-left), and posterior elevation map (down-right).

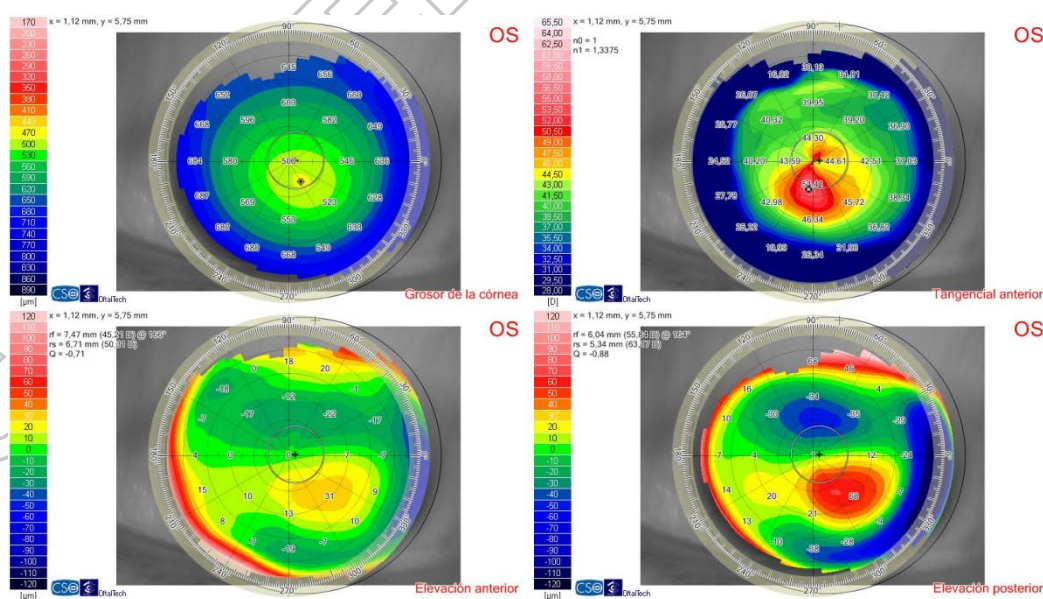


Figure 3.- Anterior corneal aberrometric analysis in a keratoconus eye with the Scheimpflug-based topography system Sirius from CSO (Italy). Six maps are displayed from left to right and from up to bottom: total aberration map, higher order aberration map, astigmatism map, primary coma map, spherical aberration and residual orders map (higher order aberrations excluding primary coma and spherical aberration).

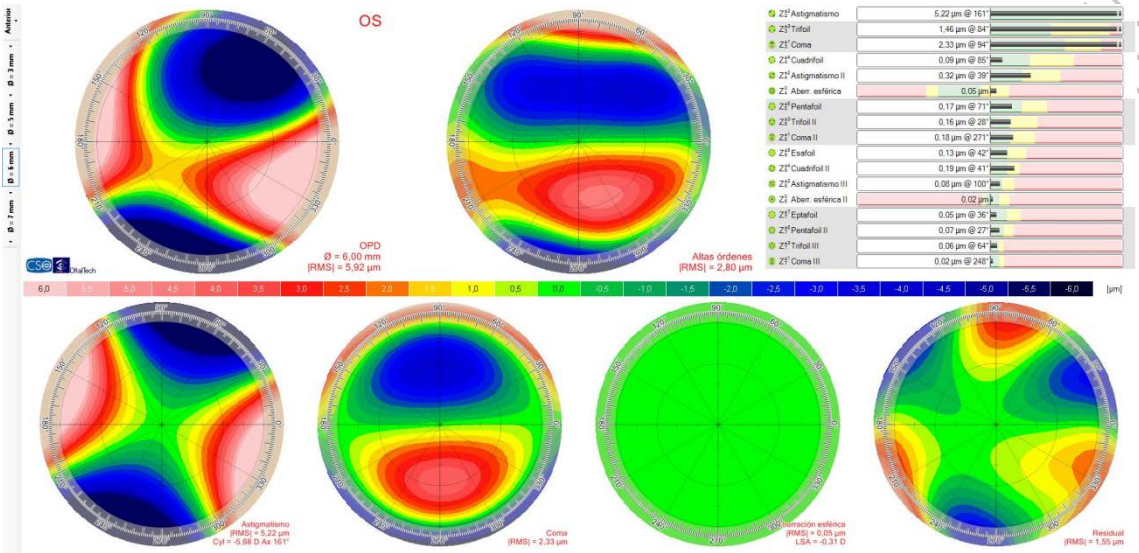


Figure 4.- Pseudokeratoconus due to an alteration of the tear film during the measurement procedure. Specifically, there was a break of tear film in the supero-nasal quadrant leadin to a false appearance of flattening and the consequently steepening of the cornea in the infero-temporal quadrant.

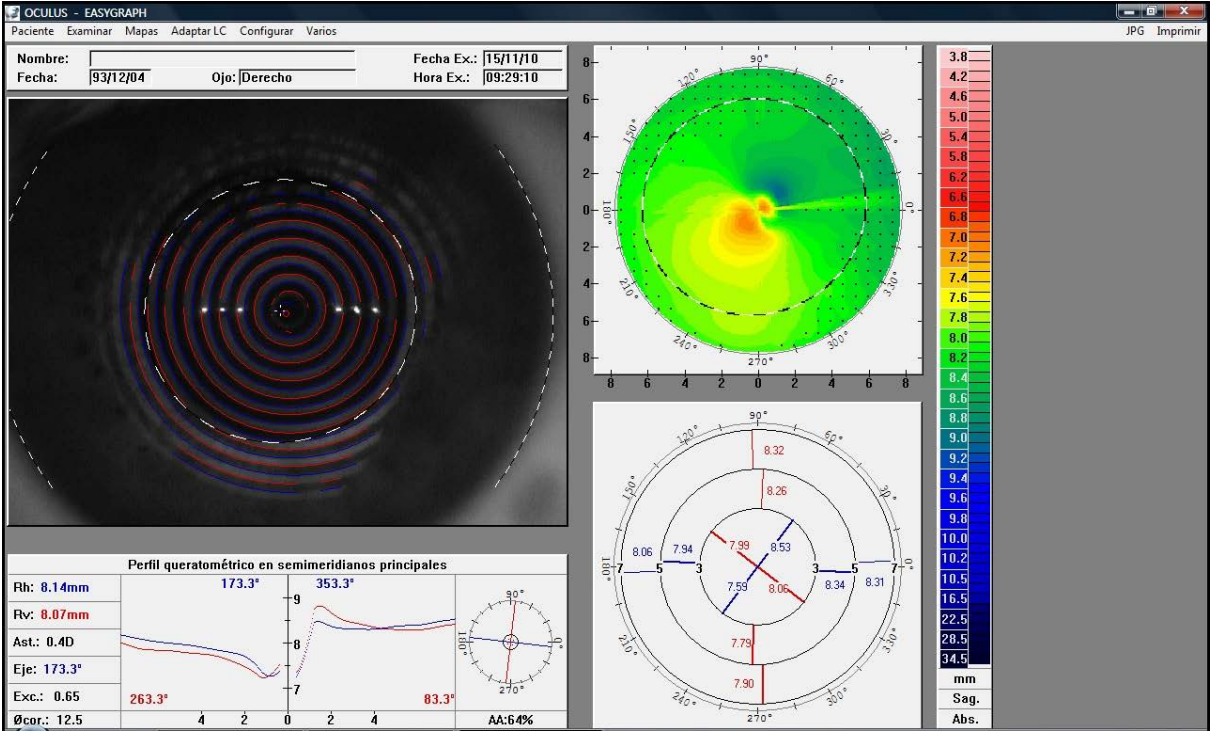


Figure 5.- Topographic map showing an infero-superior corneal asymmetry compatible with a pattern of keratoconus suspect in a patient wearing a silicone hydrogel contact lens. This map was normalized after the cessation of the lens during 1 week, suggesting that there was a superior pressure of the lens in the superior part of the corneal leading to this corneal asymmetry.

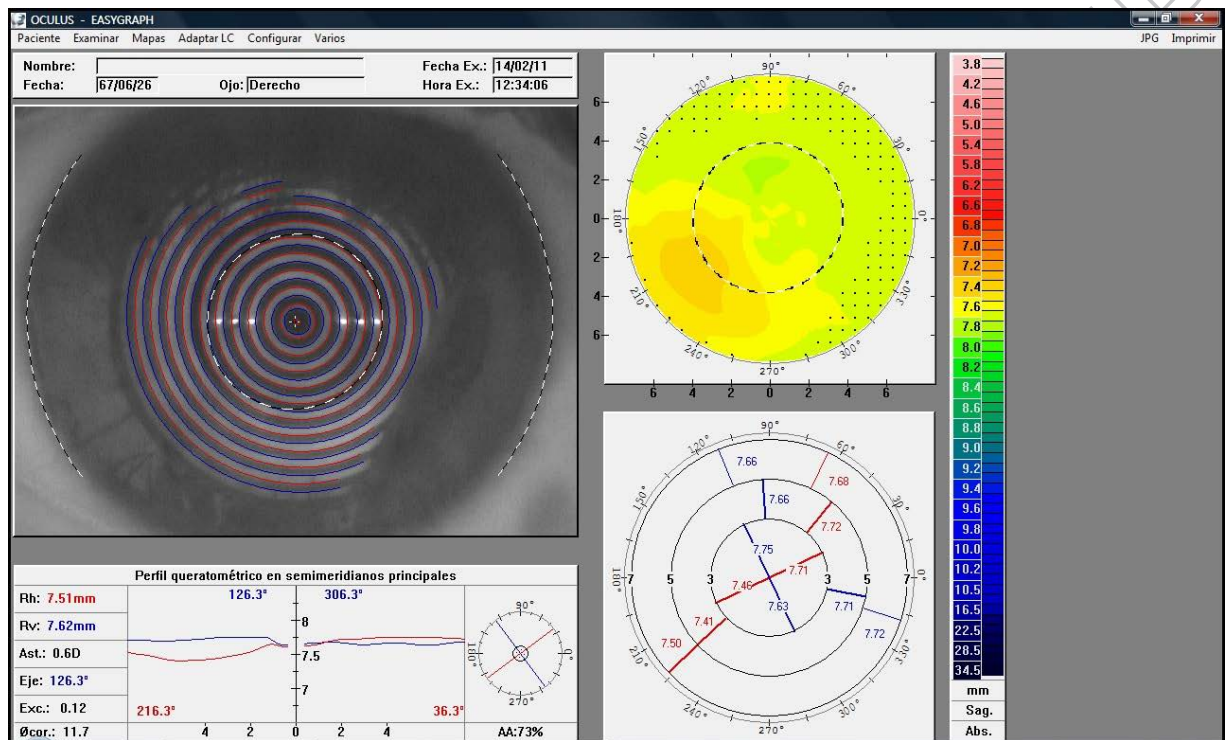


Figure 6.- Corneal topographic map showing an infero-superior asymmetry compatible with a keratoconus in a cornea with a superior scar due to a trauma.

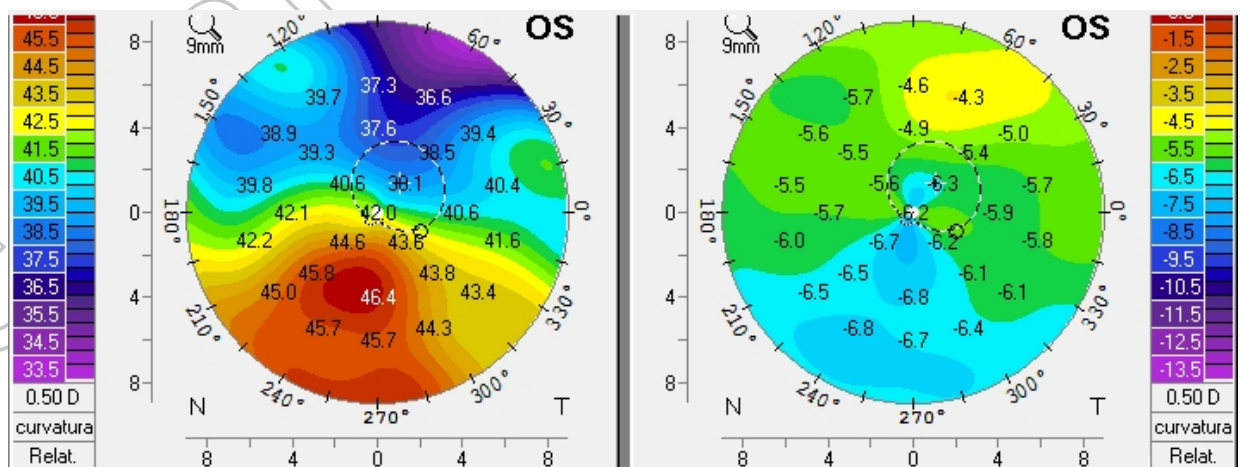


Table 1.- Diagnostic criteria reported for different topographic parameters.

Parameter	Cutoff or diagnostic criteria	Sensitivity	Specificity
Surface Asymmetry Index (SAI)	> 1		
Corneal Irregularity Measurement (CIM)	1.10 to 5.00 μm		
Infero-superior (I-S) asymmetry	> 1.8 D		
KISA %	≥ 100		
Keratoconus Prediction Index (KPI)	≥ 0.38	86%	100%
Mean keratometry (KM) + I-S	KM > 47.8 D I-S > 1.9 D	96%	85%
Mean toric keratometry (MTK)	From 36.0 to 41.7 and from 47.3 to 60.0 D		
Surface Regularity Index (SRI)	> 1.55		
Keratoconus Index (KCI)	> 0%	98%	99%
High rate of steepening (HRS)	1.40 D/mm	95.7%	96.4%
Index of surface variation (ISV)	≥ 0.37 suspicious ≥ 0.41 pathological		
Index of vertical asymmetry (IVA)	≥ 0.28 suspicious ≥ 0.32 pathological		
Keratoconus Index (KI)	> 1.07		
Center Keratoconus Index (CKI)	≥ 1.03		
Smallest radius of curvature (RMin)	< 6.71		
Index of height asymmetry (IHA)	≥ 19 suspicious > 21 pathological		
Index of height decentration (IHD)	≥ 0.014 suspicious > 0.016 pathological		
Aberration coefficient (ABR)	≥ 1		
Topography disparity (TD)	1.64	93.3%	92.1%